Armed Forces College of Medicine

AFCM

كلية الطب بالقوات المسلحة
Armed Forces College of Medicine

Diabetes Mellitus (Integrated Lecture 2)

Integrated Departments

- **Pharmacology:** Prof. Omayma Khorshid
- **Internal medicine**: Assist.Prof. Nesma Ali

Intended Learning Outcomes (ILOs)

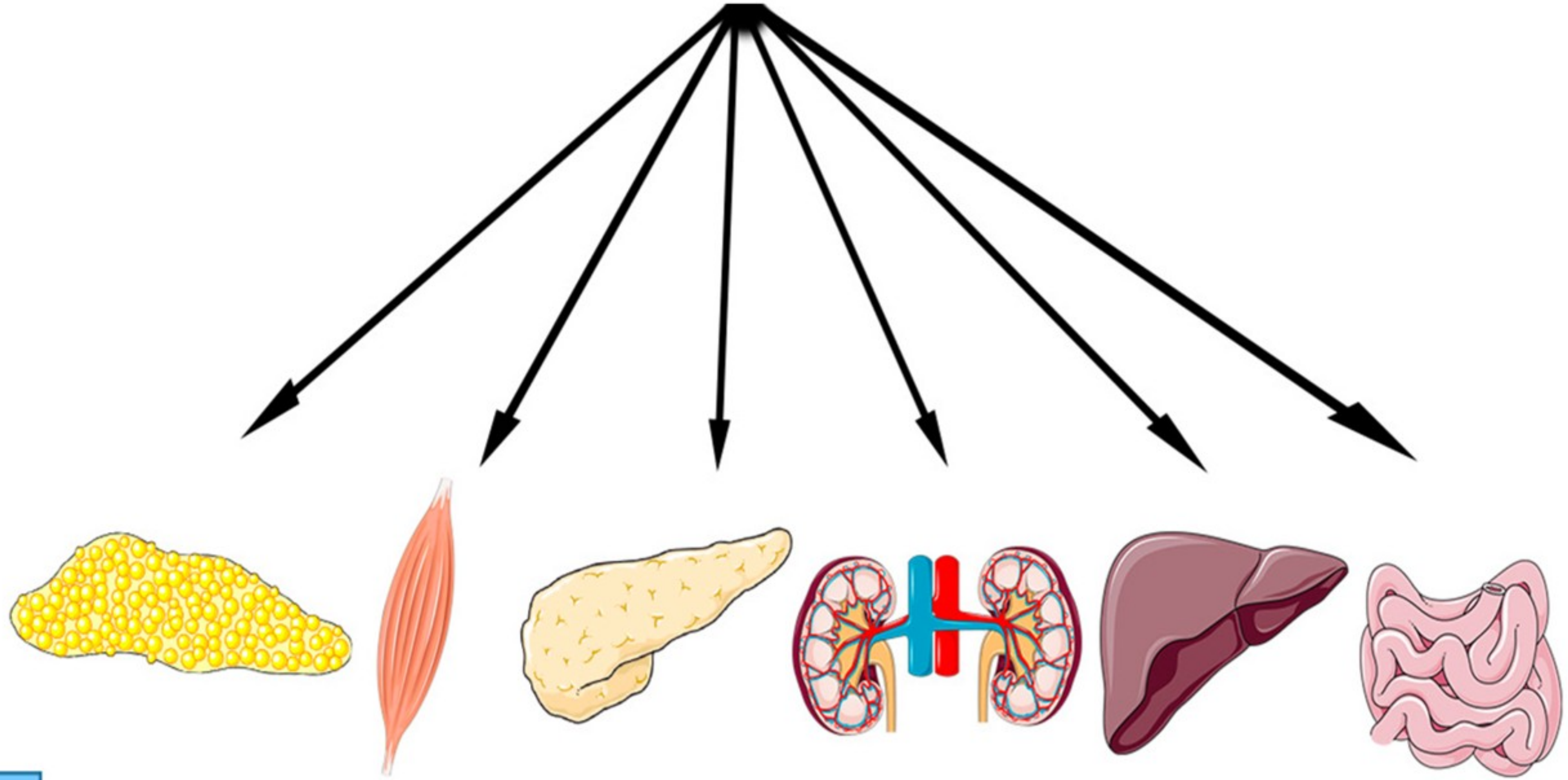
By the end of this lecture the student will be able to:

1. **Classify the antidiabetic drugs used in the treatment of type 2 diabetes mellitus (Pharmacology)**
2. **Explain the different mechanisms of action of the antidiabetic drugs used in the treatment of type 2 diabetes mellitus (Pharmacology)**
3. **Identify the adverse effects of the antidiabetic drugs (Pharmacology)**
4. **List glycemic goals for patients with diabetes mellitus (Internal Medicine)**
5. **Management of diabetes mellitus (Internal Medicine)**

Armed Forces College of Medicine

Anti-diabetic Drugs in Type 2 DM

Main effects of currently used anti-diabetic Drugs



Target Tissues	Adipose tissue Skeletal muscle	Pancreas	Kidney	Liver	Intestine
Primary Effects	↑ Peripheral Glucose Uptake	↑ Insulin Secretion	↓ Glucose Reabsorption	↓ Glucose Introduction	↓ Glucose Absorption
Class of Medication	Biguanides Thiazolidinediones	Sulfonylureas Meglitinides	SGLT2 inhibitors	Biguanides Thiazolidinediones	α-glucosidase inhibitors

Incretin Mimetics & Enhancers

https://www.google.com.eg/url?sa=i&url=https%3A%2F%2Fwww.researchgate.net%2Ffigure%2FTarget-tissues-and-mechanism-of-action-of-current-anti-diabetic-drugs_fig1_319438706&psig=AOvVaw0VetCf-rytmv7Pqm1Ypq6s&ust=1587441375909000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCMCagY2O9ugCFQAAAAAdAAAAABAD

Anti-diabetic Drugs

- **Insulin secretagogues** ***(Increase insulin release)***

  Sulfonylureas or Meglitinides (Glinides).
- **Insulin sensitizers** ***(improve insulin action)***

  Biguanide (metformin)or ***ThiaZolidineDiones****(Glitazone*
- **Modify intestinal absorption of carbohydrate**

  Alpha-glucosidase inhibitor.
- **Incretin Mimetics & Enhancers**

  GLP-1 analogs and DPP-4 inhibitors
- **Sodium-glucose cotransporter 2(SGLT2) inhibito**

  Canagliflozin & Dapagliflozin ***(Renal glucose reabsorptio***

  ↓

Insulin Secretagogues

1) Sulfonylureas

2) Meglitinides (Glinides)

1) Sulfonylurea Group

A) First Generation

Short acting

Acetohexamide

Intermediate acting

Chlorpropamide (up to 60 hours) √√√

Used in pituitary diabetes insipidus (↑ADH)

Long acting

1) Sulfonylurea Group

B) Second Generation

More potent &Less side effects

Intermediate acting → up to 24 hrs

1- Glibenclamide [Glyburide] ***(Daonil)***

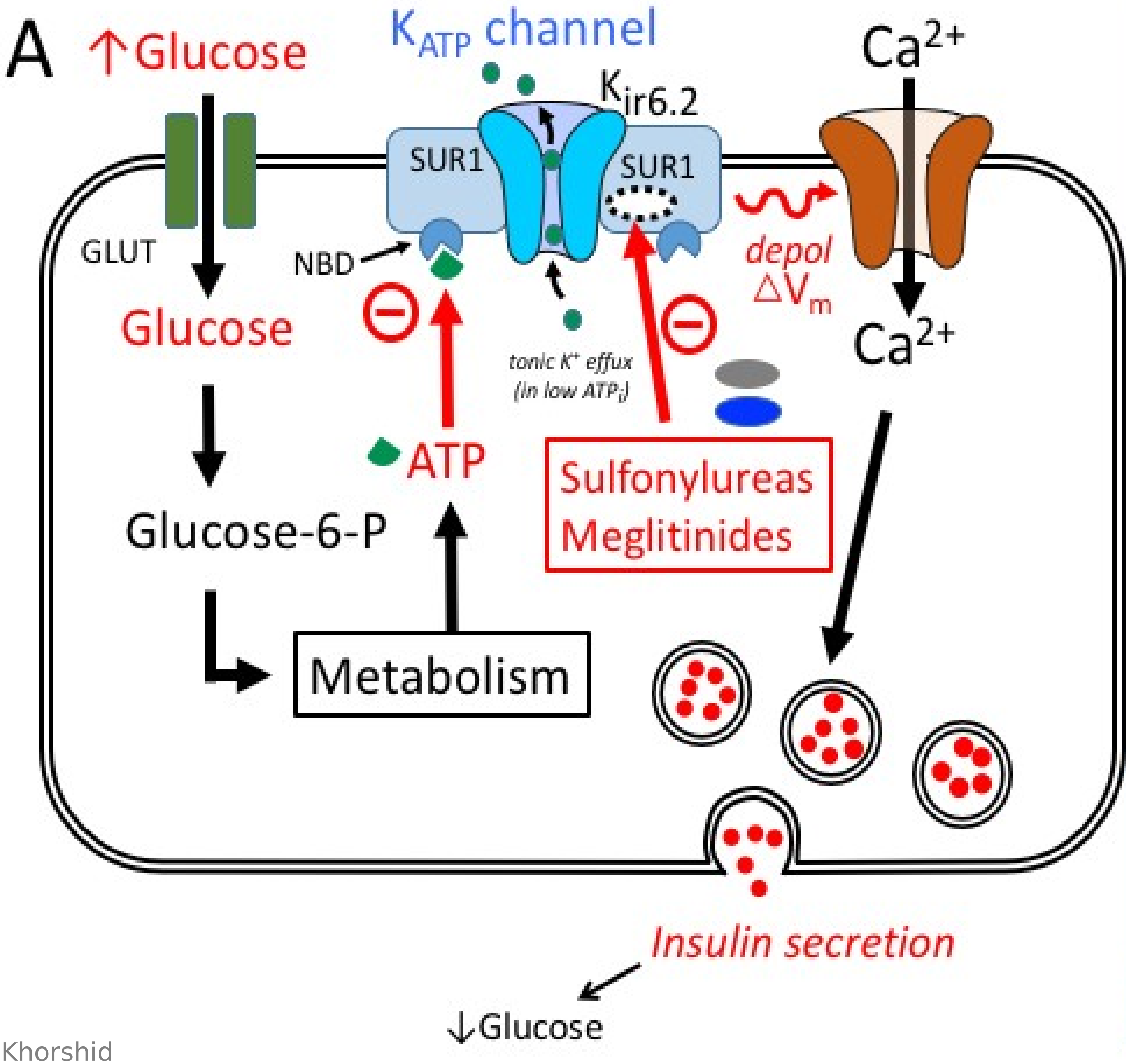
2- Glipizide ***(Minidiab),***

3- Gliclazide ***(Diamicrone)***

4- Glimepiride (Amaryl)

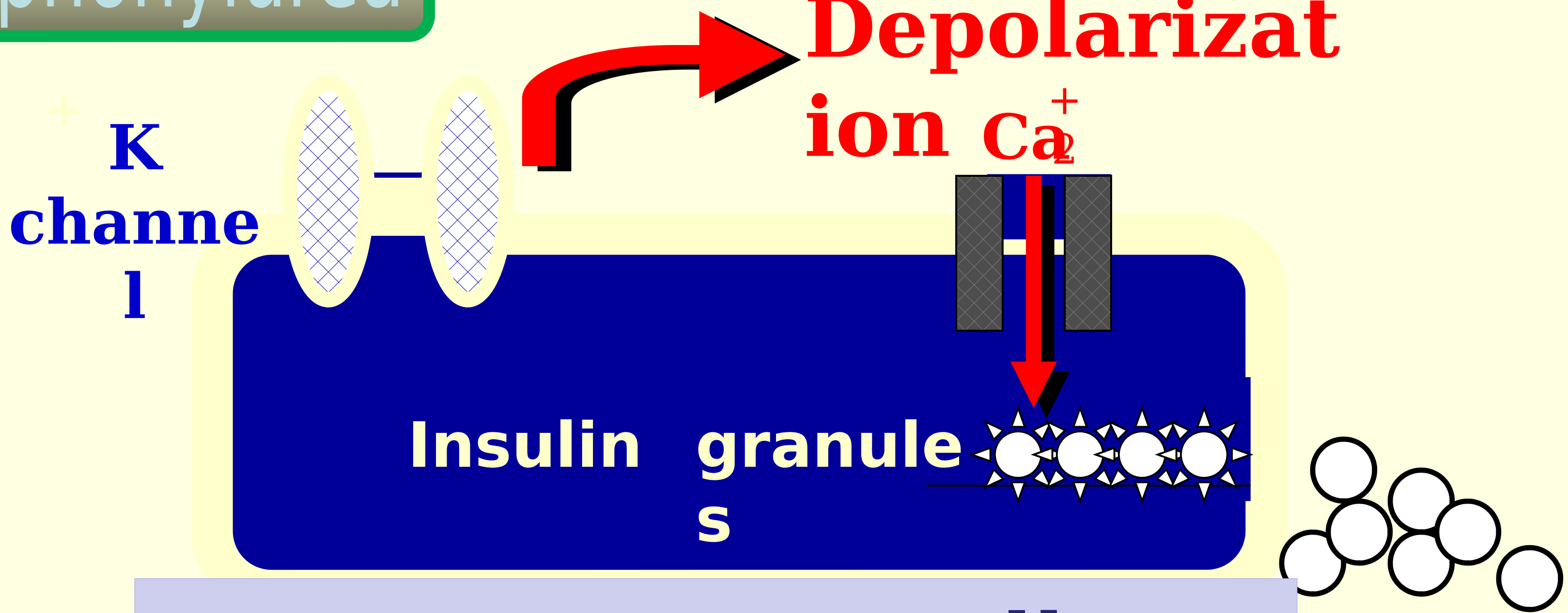
the most potent

Sulfonylurea Group: **Mechanism of action**



Sulphonylurea

Mechanism of action



Increase Insulin Release

Sulfonylur … **or (SUR1) subunit,** in the pancreatic **β-cell** membrane causing a conformational change that **blocks the ATP- dependent K channels** causing **depolarization** that results in **Ca influx** and **enhanced insulin release from pancreatic β-cells.**

N.B. Insulin secretagogues are not effective in patients who lack functional pancreatic B cells.

Pharmacokinetics

- Given **orally** □ **duration 12-24 h**
- **Bind** to serum proteins --- drug interactions
- **Hepatic Metabolism**
- **Excreted in urine & feaces**.

Adverse effects

- **Hypoglycemia.**
- **Weight gain.**
- **1ry and 2ry failure of sulfonylureas.**
- **The Sulfonylureas Traverse the Placenta**

(deplete *insulin* from the fetal pancreas)

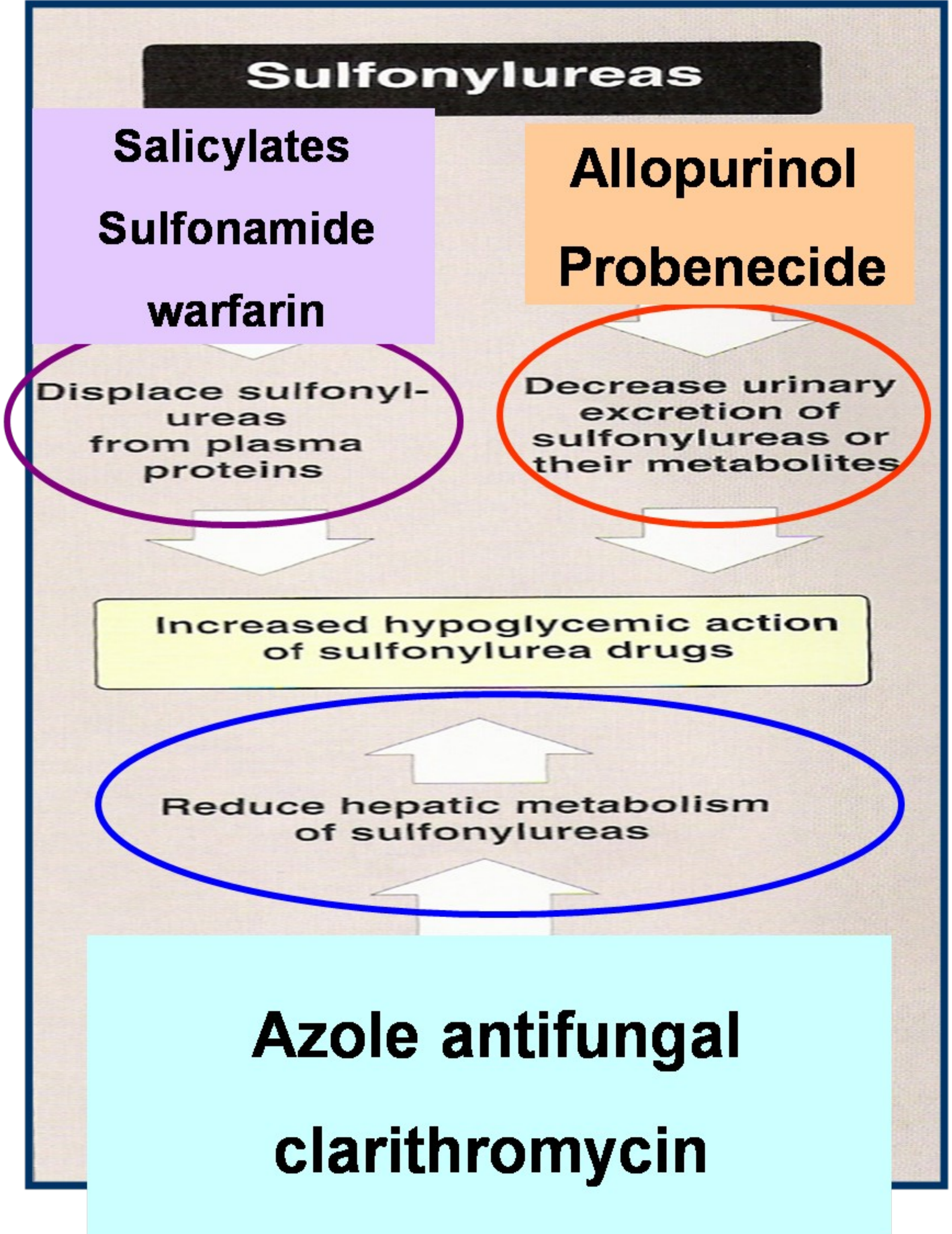
In **Diabetic Pregnant** Women the **1st choice is** ***Insulin.***

N.B. ***Glyburide*** **can be used as:**

it has minimal transfer across the placenta

- **In renal dysfunction:**

XXXX *Glyburide*



Sulfonylureas

Salicylates

Sulfonamide

warfarin

Displace sulfonylureas from plasma proteins

Allopurinol

Probenecide

Decrease urinary excretion of sulfonylureas or their metabolites

Increased hypoglycemic action of sulfonylurea drugs

Reduce hepatic metabolism of sulfonylureas

Azole antifungal

clarithromycin

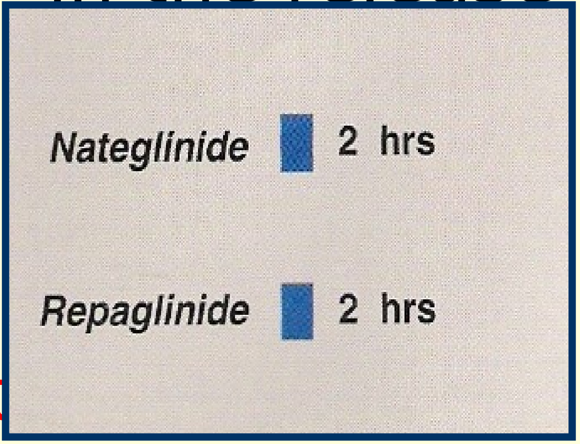
INSULIN SECRETAGOGUES

2) Meglitinides (Glinides)

- Includes ***Repaglinide*** and ***Nateglinide.***
- Although **they are not sulfonylureas**, they **have common actions & mechanism .**

Mechanism of action

- They bind to a distinct site on the sulfonylurea receptor of ATP-sensitive potassium channels, thereby initiating a series of reactions resulting in the release of *insulin.*



- The ***Glinides*** have a
  rapid onset and short durat
  (Before Each Meal)
  (lower incidence of hypoglycemia)

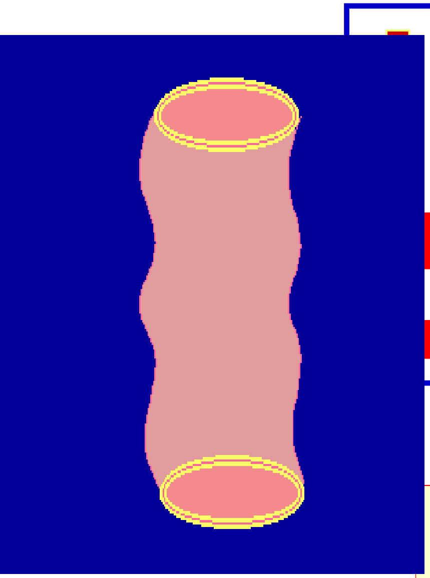
Insulin Sensitizers

1) **Biguanides (Metformin)**

2) **Glitazones**

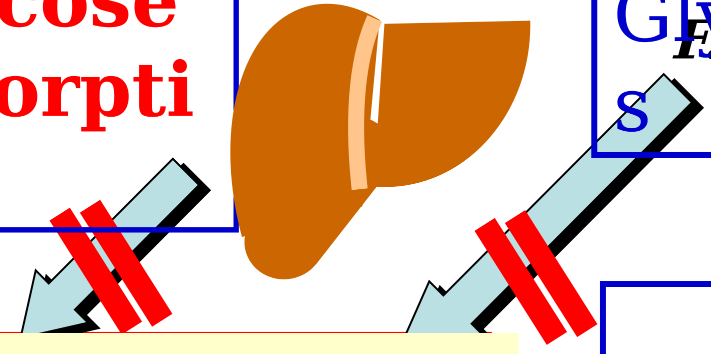
“ThiaZolidineDiones” TZD

Biguanides **Metformin**



lucose bsorption

Glycogen



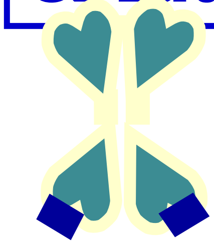
Glycogenolysis

F.F.A.'s and A.A.'s

Hepatic gluconeogenesis

Euglycemic

Uptake and utilization of glucose by muscle & fat cells



Increase insulin binding (to receptors) &action

Adverse effects

1) Gastrointestinal [anorexia□reduce weight ,nausea, vomiting & diarrhea].

2) If Long term treatment: ↓ Vit. B12 absorption

3) **Rarely** **fatal lactic acidosis** may occurr So,

Metformin is contraindicated in diabetics with:

- Renal disease
- Hepatic disease
- CHF COPD

Insulin Sensitizers

2) Glitazones

“ThiaZolidineDiones”

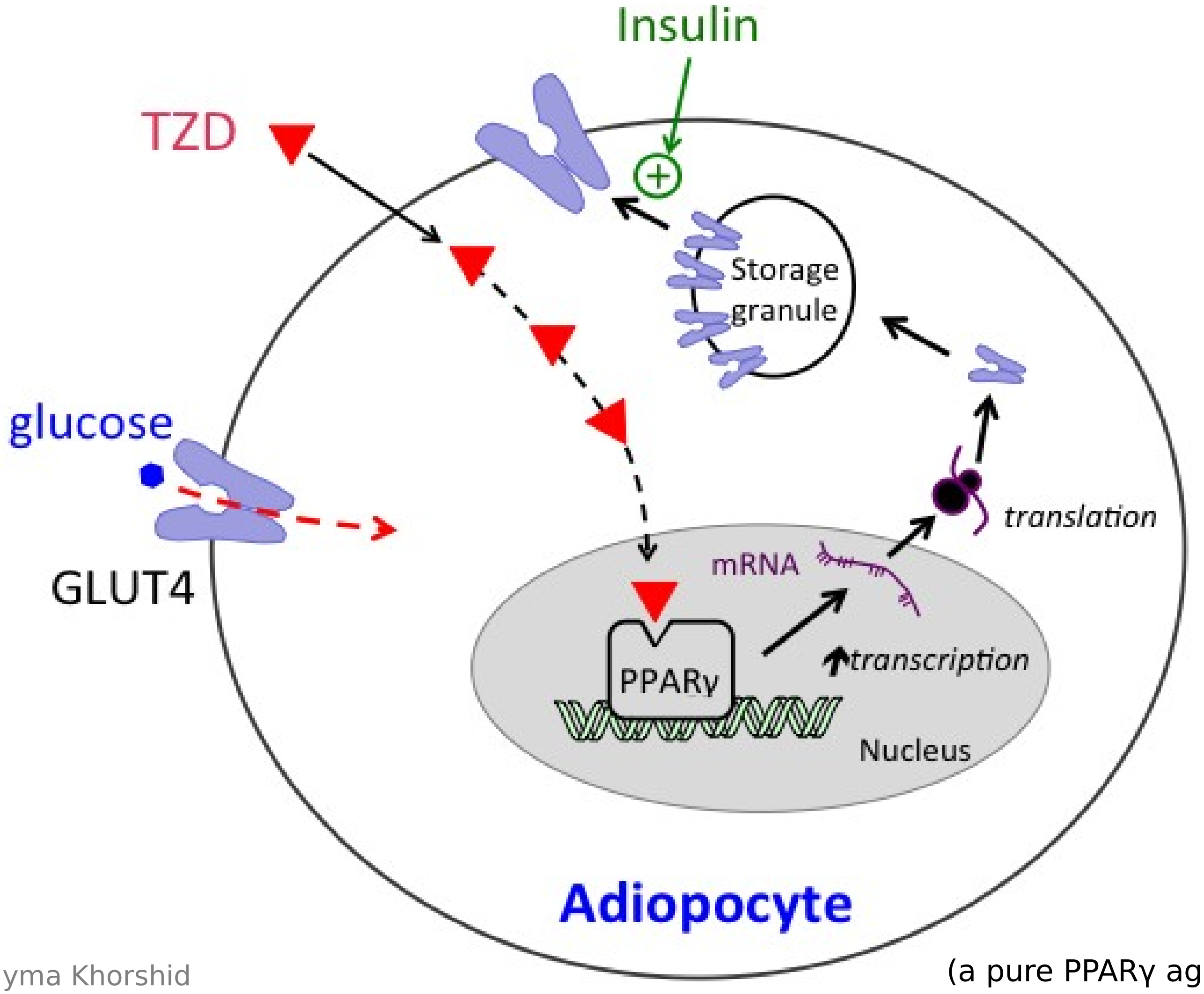
TZD

Troglitazone
Pioglitazone
Rosiglitazone

Mechanism of action

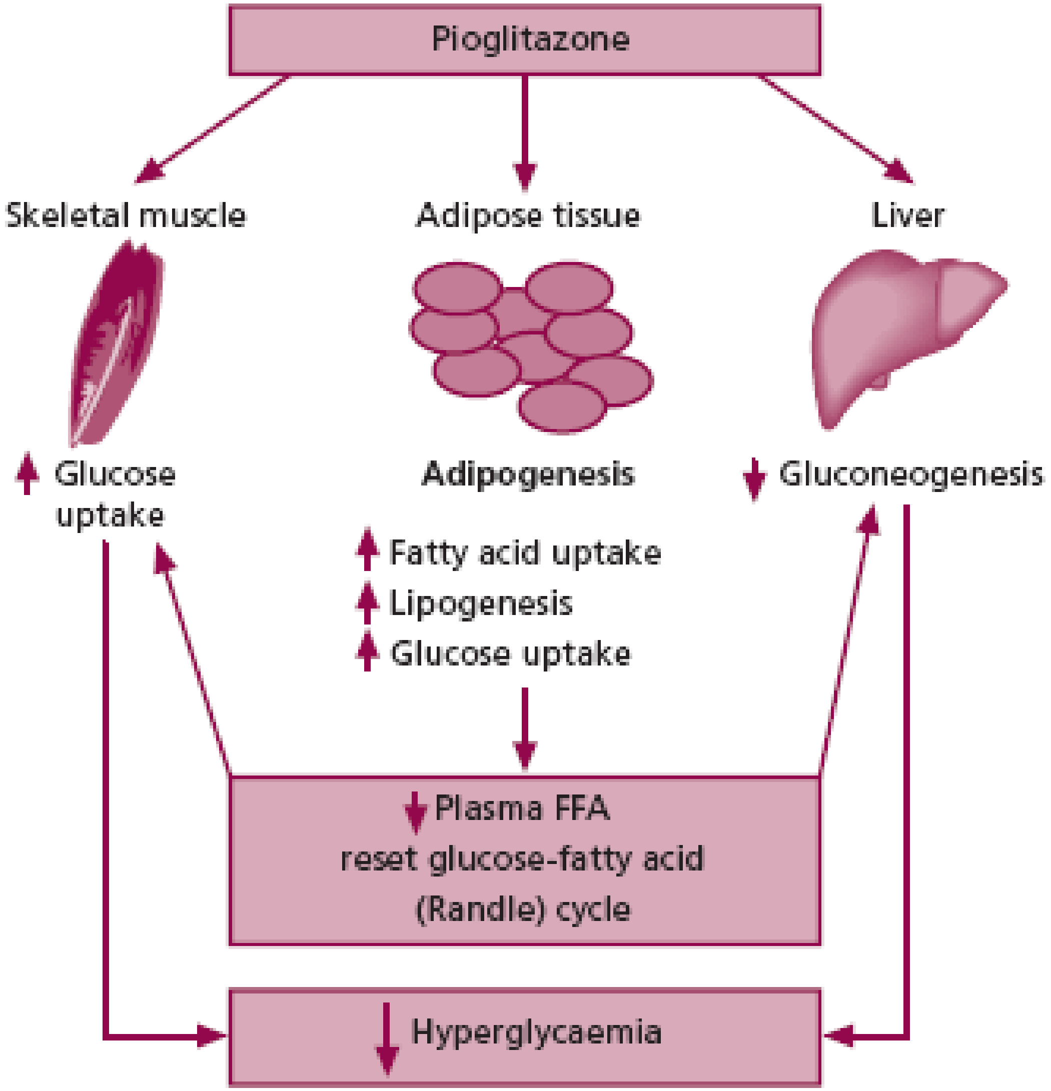
- **Target the peroxisome proliferator-activated receptor-γ (PPAR-γ) a nuclear hormone receptor.**
- ***Activation of PPAR-γ receptors regulates the transcription of several insulin responsive genes***
- **So *they* ↑↑ *insulin sensitivity* in *adipose tissue, liver,* and *skeletal muscle* (in which PPAR-γ receptors are found).**

Mechanism of action



(a pure PPARγ agonist)(McCulloch, 2016).

Medscape® www.medscape.com



Key: FFA = free fatty acids

Adapted with permission from Bailey CJ, Feher MD, Therapies for Diabetes, Sherborne Gibbs, Birmingham UK, 2004

Source: Br J Diabetes Vasc Dis © 2006 Sherbourne Gibbs, Ltd.

Adverse effects

1) **Hepatotoxicity:** **Troglitazone???**

Liver enzyme levels should be **measured** initially, then every 2 months for a year, and periodically thereafter.

- **Weight gain:** [due to increase SC fat & fluid retention]

  so avoided In severe heart failure ⬆ (Fluid retention)

- **Rosiglitazone : potential increased risk of M.I?? LDL & TG**

- ***Glitazones* : associated with increased fracture**

α-Glucosidase Inhibitors
Acarbose and Miglitol

Mechanism of action:

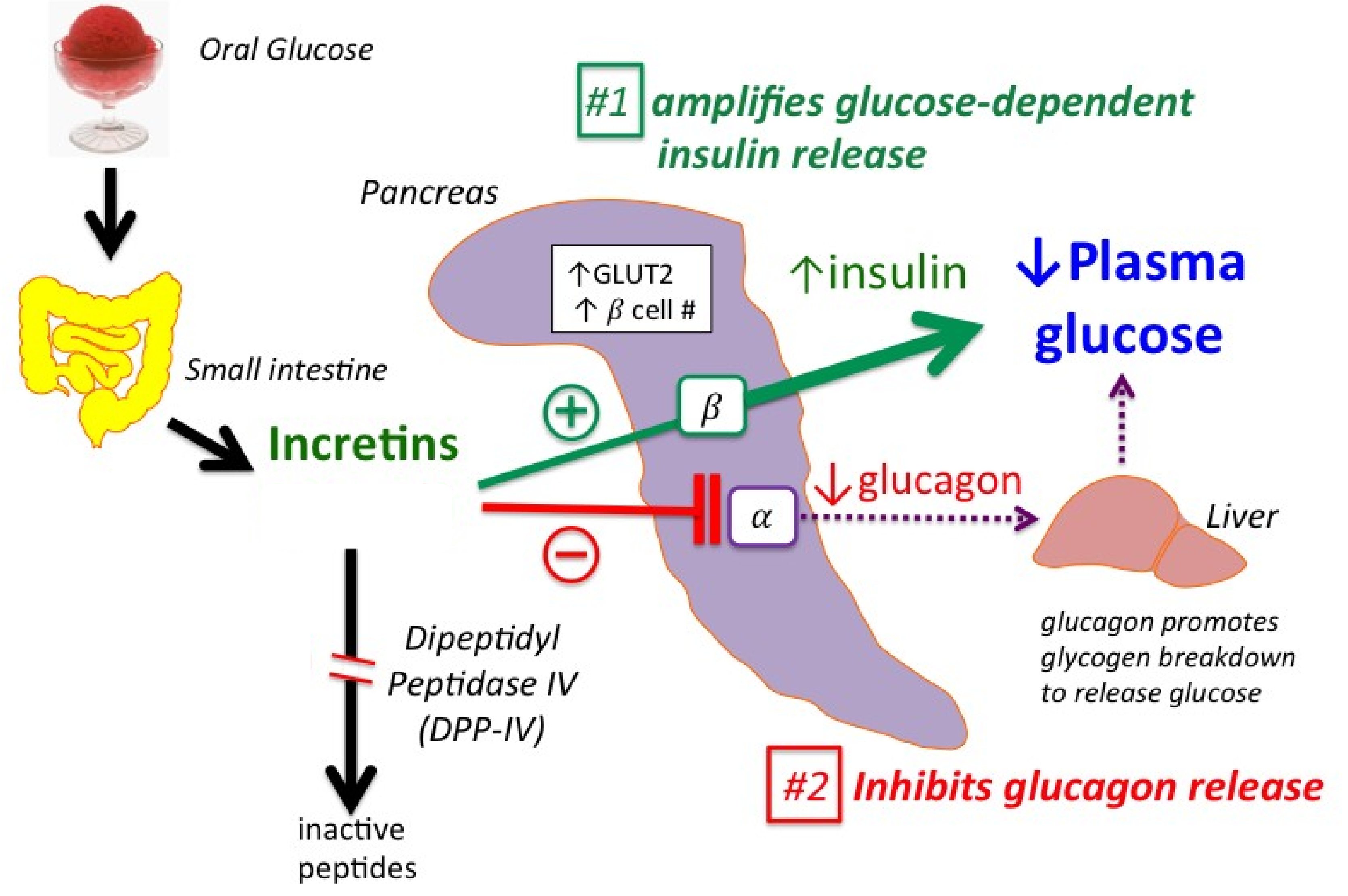
- Orally active --- **Miglitol is 5-6 times > potent**
- Reversibly inhibiting membrane-bound -glucosidase in the intestinal brush border thereby decreasing glucose absorption.
- **The postprandial rise of blood glucose is blunted.**

- Decrease the bioavailability of ***metformin*** *so* concurrent use *should be* ***AVOIDED***

Incretin Mimetics & Enhancers

- **Incretins are peptide hormones that originate in the gastrointestinal tract. They are released during nutrient absorption, augmenting insulin secretion. reduce postprandial glucagon secretion and delay gastric emptying time.**
- **Glucagon-like peptide-1 (GLP-1) is one of the incretins.**

Incretin Mimetics & Enhancers


Oral Glucose
#1 amplifies glucose-dependent insulin release
Pancreas
↑GLUT2
↑ β cell #
↑insulin
↓Plasma glucose
Small intestine
Incretins
+
β
α
−
↓glucagon
Liver
glucagon promotes glycogen breakdown to release glucose
Dipeptidyl Peptidase IV (DPP-IV)
inactive peptides
#2 Inhibits glucagon release

* Physiological $t_{1/2} \approx 2$ mins due to rapid inactivation by DPP-IV

https://www.google.com.eg/url?sa=i&url=http%3A%2F%2Ftmedweb.tulane.edu%2Fpharmwiki%2Fdoku.php%2Fdpp-4_inhibitors&psig=AOvVaw1p1NqlZY1VY5-7twkFlJGn&ust=1587412355336000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCKiFw-

Incretin Mimetics
GLP-1 analogs

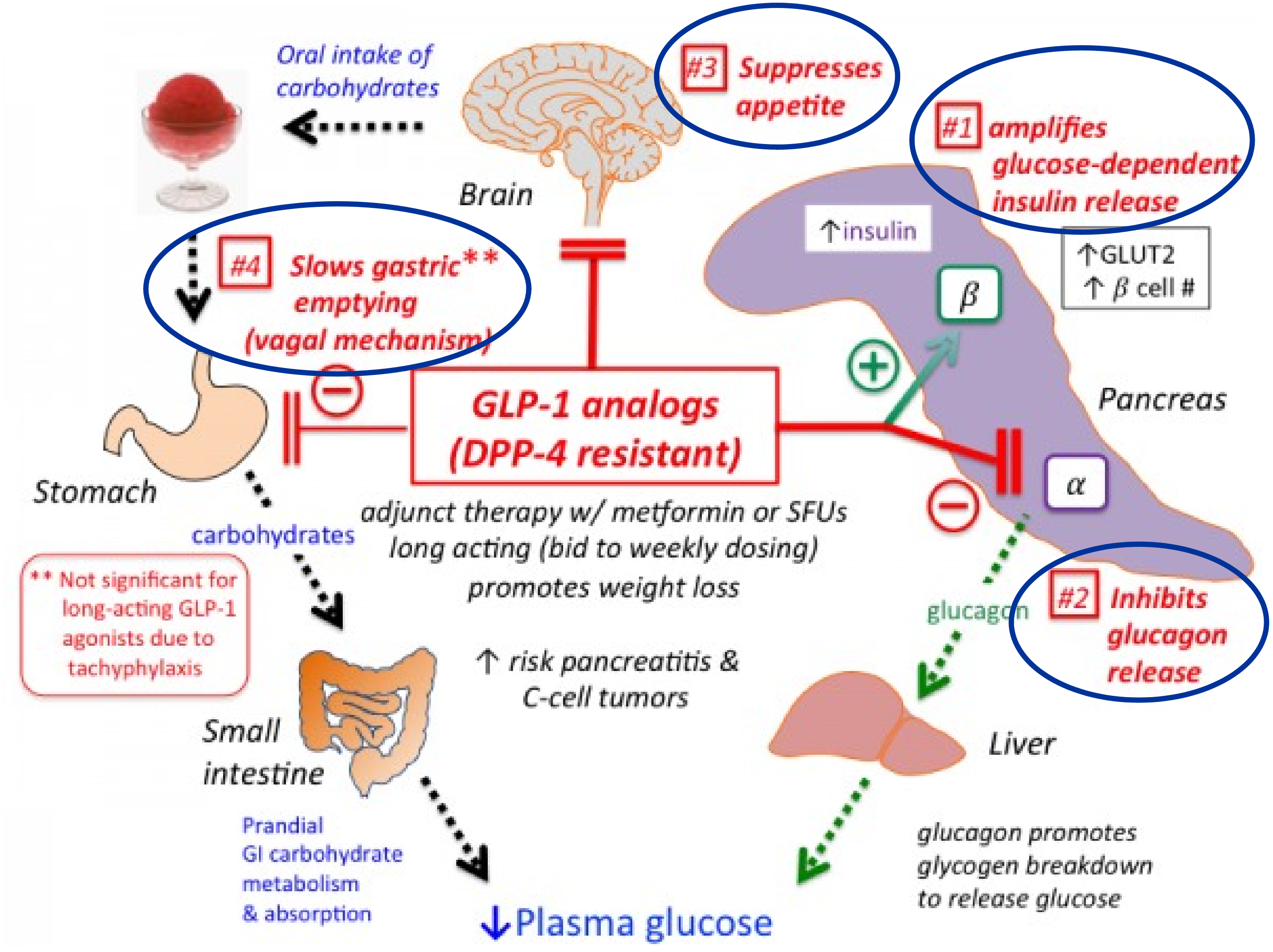
- **Exenatide** (Byetta) □ twice daily

  Exenatide extended release □ weekly
- **Liraglutide** (Victoza), taken daily

Given by SC injection

Hypoglycemia is a risk, but usually only if + another medication known to lower blood sugar.

GLP-1 analogs


Oral intake of carbohydrates
Brain
#3 Suppresses appetite
#1 amplifies glucose-dependent insulin release
↑insulin
↑GLUT2
↑ β cell #
β
#4 Slows gastric** emptying (vagal mechanism)
GLP-1 analogs (DPP-4 resistant)
Pancreas
α
Stomach
carbohydrates
adjunct therapy w/ metformin or SFUs
long acting (bid to weekly dosing)
promotes weight loss
** Not significant for long-acting GLP-1 agonists due to tachyphylaxis
glucagon
#2 Inhibits glucagon release
↑ risk pancreatitis & C-cell tumors
Small intestine
Liver
Prandial GI carbohydrate metabolism & absorption
↓Plasma glucose
glucagon promotes glycogen breakdown to release glucose

- https://www.google.com.eg/url?sa=i&url=http%3A%2F%2Ftmedweb.tulane.edu%2Fpharmwiki%2Fdoku.php%2Fexenatide&psig=AOvVaw20cobAMyqZJha7pjcFbOK4&ust=1586010845924000&source=images&cd=vfe&ved=0CAIQjRxqGAoTCLCzw6S9zOgCFQAAAAAdAAAAABDJAQ

GLP-1 analogs

Exenatide (BYETTA)

- Synthetic analog of glucagon-like peptide1 (GLP-1).
- Improve blood sugar control by mimicking the action of glucagon-like peptide 1 (GLP-1) and act through the GLP-1 receptor.
- **improves insulin secretion** from β cell of pancrease

- **↓ postprandial glucagon release**
- **slows gastric emptying time(↓ absorption of some drugs)**

- **Parenteral SC add on to oral treatment of**

GLP-1 analogs

GLP-1 analogs cause **weight loss** due to:

- They suppress appetite.
- They reduce the food intake by enhancing satiety (delay the movement of food from the stomach to small intestine)

- Some of **GLP-1 analogs results in** improvements in the blood pressure, cholesterol and triglyceride levels. This may be due to the control of blood sugar and weight loss.

- **Liraglutide** is a **useful therapy in patients with** advanced **type 2 diabetes complicated by cardiovascular disease**, except patients with severe

Incretin Enhancers

Dipeptidyl peptidas-4 (DPP-4) inhibitors

- ***Orally***
- Inhibits metabolic inactivation of endogenous GLP-1, **indirectly:**
  - ↑ glucose-dependent insulin release.
  - ↓ postprandial glucagon release.
- **Preparations:**

➢ **Sitagliptin (JANUVIA)**

➢ **Linagliptin□ in renal dysfunction (NO dose readjustment)**

(elimenated via enterohepatic system)

➢ **Saxagliptin ??□** impaired cardiac contractility□ **HF ??**

ALL are Available in combination with metformin

FDA-approved SGLT2* Inhibitors

Canagliflozin (Invokana)

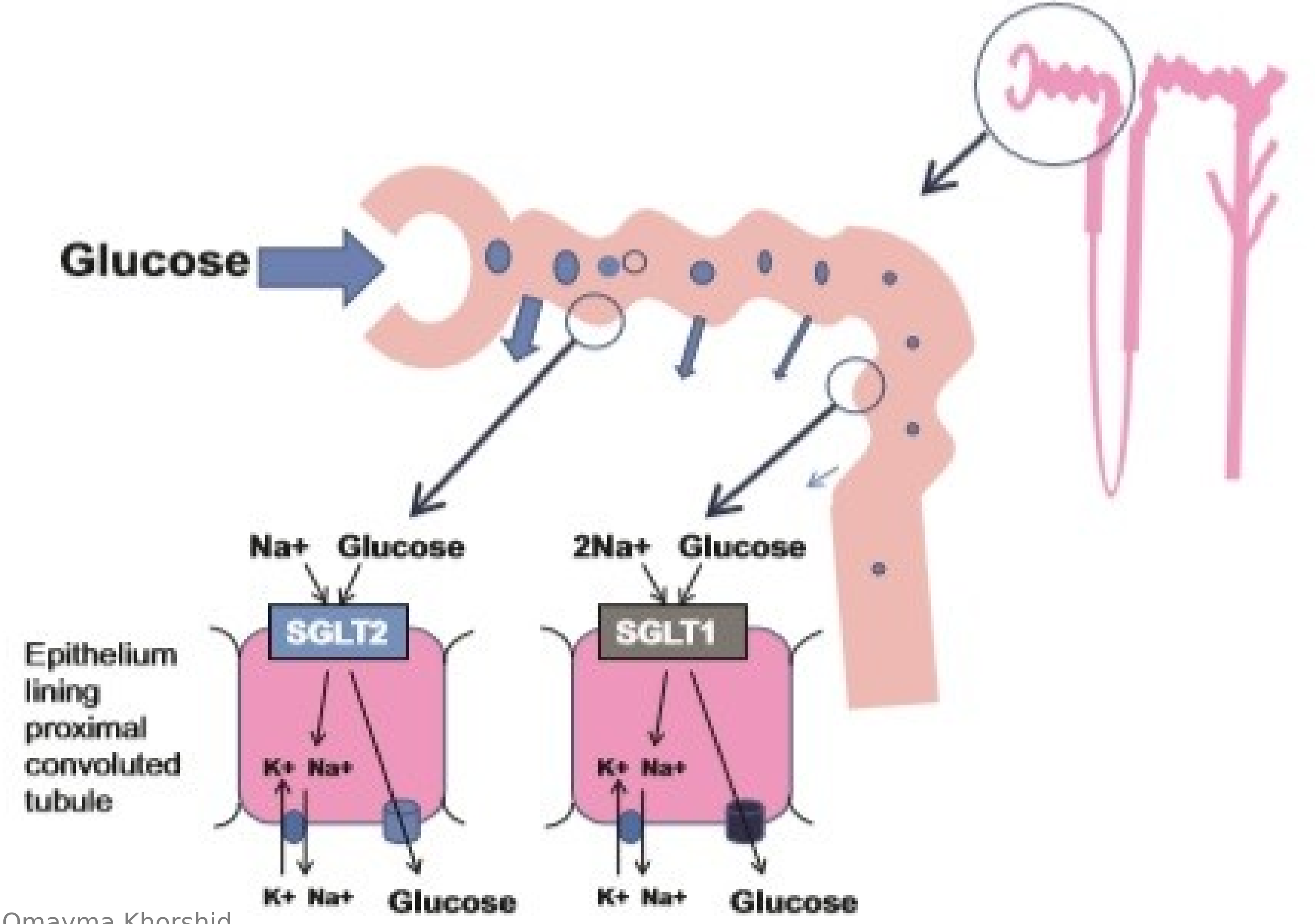
Dapagliflozin (Farxiga)

Empagliflozin (Jardiance)

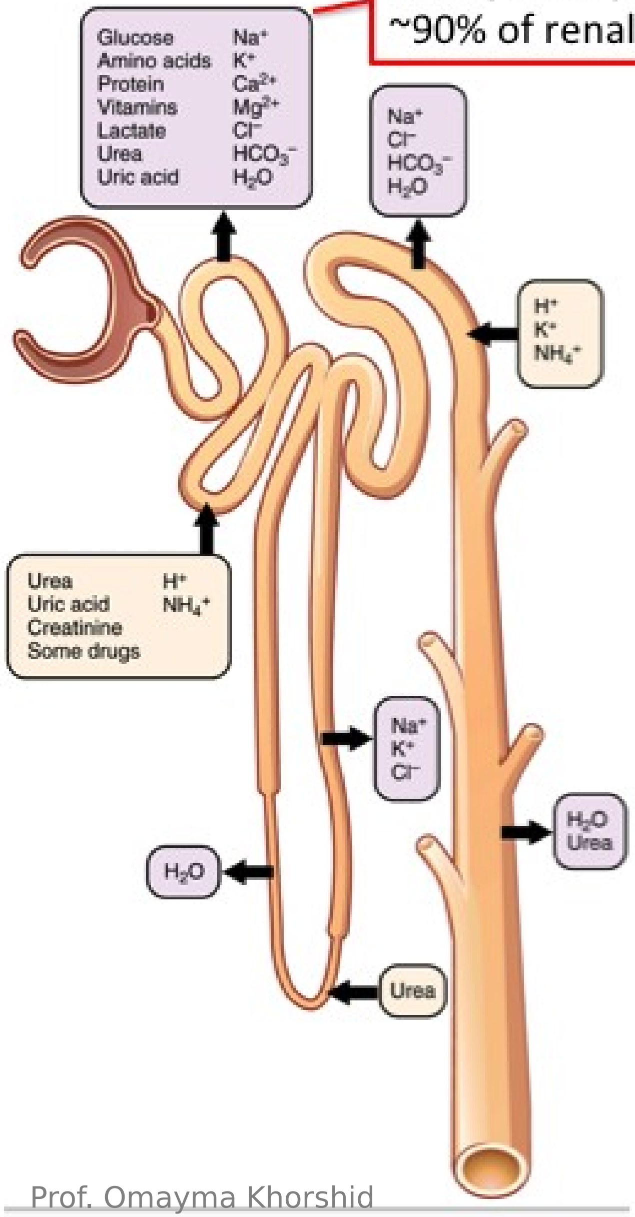
*Sodium-glucose cotransporter 2

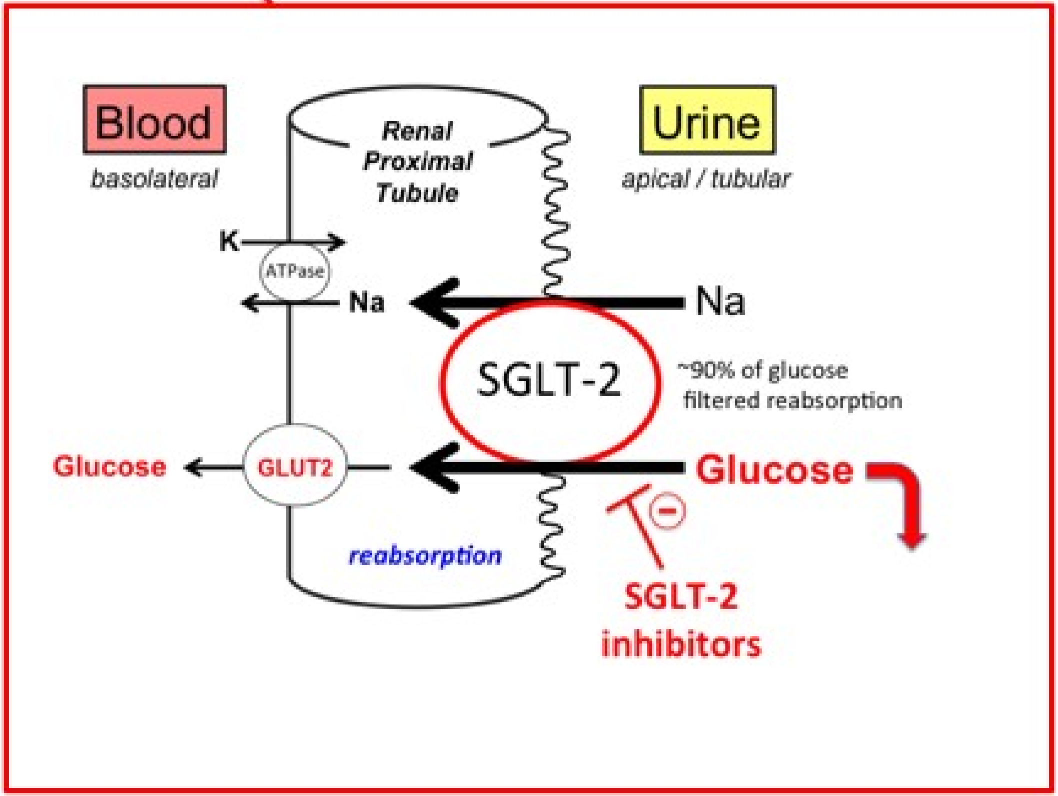
FIGURE 1: SGLT MEDIATED GLUCOSE EXCRETION IN THE RENAL TUBULE

Reproduced with permission from Bailey & Day, 2010 [7]



S1 segment proximal tubule:
~90% of renal glucose reabsorption





http://tmedweb.tulane.edu/pharmwiki/lib/exe/fetch.php/sglt2.png

NEW:
Sodium-glucose cotransporter 2 inhibitors

Gliflozins: ***Canagliflozin & Dapagliflozin***

Mechanism of action:

- **The sodium-glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney.**
- **By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose.**
- **Inhibition of SGLT2 also decreases reabsorption of sodium and causes osmotic diuresis.**
- **SGLT2 inhibitors may reduce systolic blood pressure.**
- ***However, they are not indicated for the treatment of hypertension. .***

NEW:

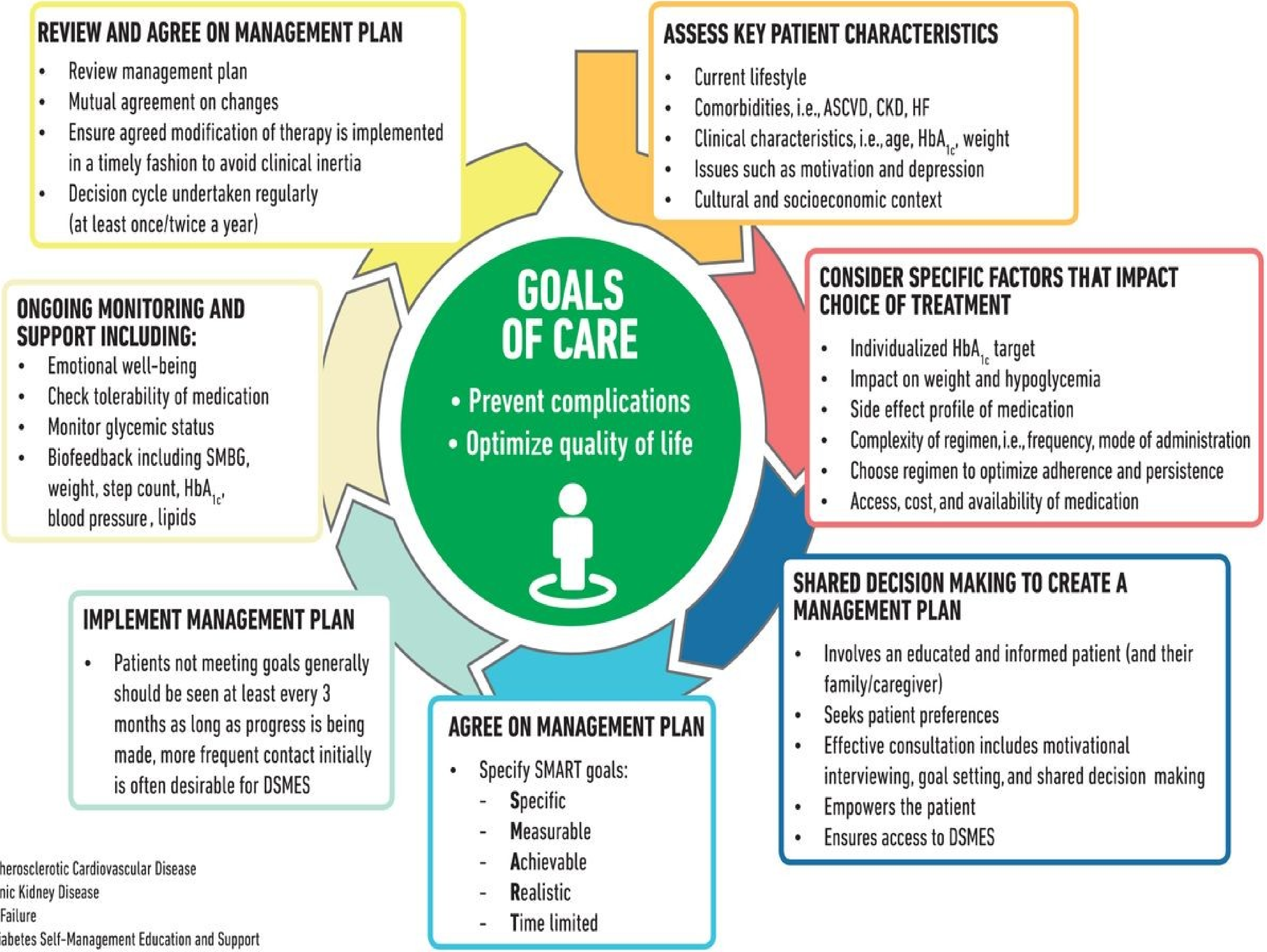
Sodium-glucose cotransporter 2 inhibitors

Gliflozins: ***Canagliflozin & Dapagliflozin***

Adverse effects:

The most common

- **female genital mycotic infections (for example, vulvovaginal candidiasis)**
- **urinary tract infections, and urinary frequency.**
- **Hypotension has also occurred, particularly in the elderly or patients on diuretics. Thus, volume status should be evaluated**



GOALS OF CARE

- Prevent complications
- Optimize quality of life

ASSESS KEY PATIENT CHARACTERISTICS

- Current lifestyle
- Comorbidities, i.e., ASCVD, CKD, HF
- Clinical characteristics, i.e., age, HbA_{1c}, weight
- Issues such as motivation and depression
- Cultural and socioeconomic context

CONSIDER SPECIFIC FACTORS THAT IMPACT CHOICE OF TREATMENT

- Individualized HbA_{1c} target
- Impact on weight and hypoglycemia
- Side effect profile of medication
- Complexity of regimen, i.e., frequency, mode of administration
- Choose regimen to optimize adherence and persistence
- Access, cost, and availability of medication

SHARED DECISION MAKING TO CREATE A MANAGEMENT PLAN

- Involves an educated and informed patient (and their family/caregiver)
- Seeks patient preferences
- Effective consultation includes motivational interviewing, goal setting, and shared decision making
- Empowers the patient
- Ensures access to DSMES

AGREE ON MANAGEMENT PLAN

- Specify SMART goals:
  - **S**pecific
  - **M**easurable
  - **A**chievable
  - **R**ealistic
  - **T**ime limited

IMPLEMENT MANAGEMENT PLAN

- Patients not meeting goals generally should be seen at least every 3 months as long as progress is being made, more frequent contact initially is often desirable for DSMES

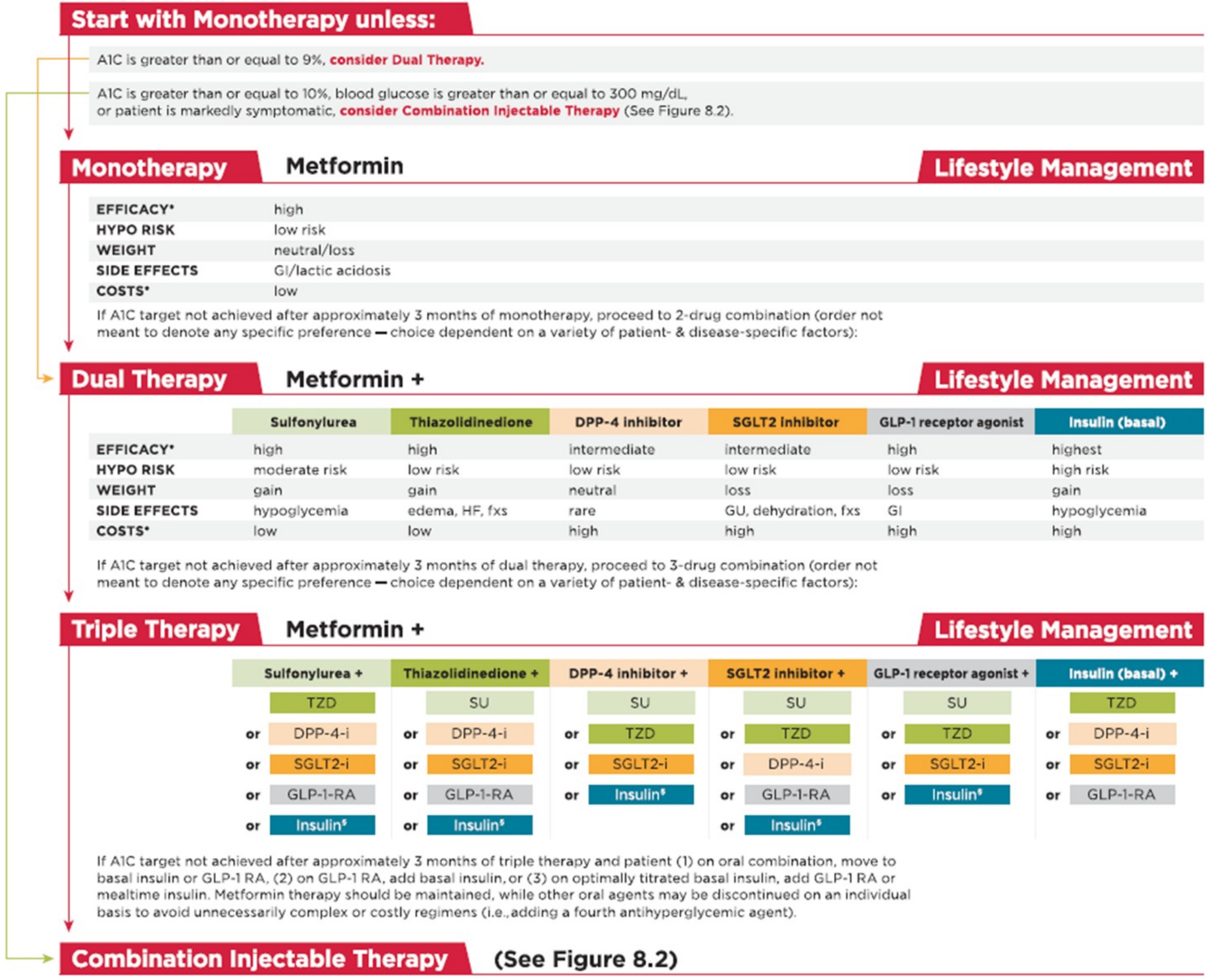
ONGOING MONITORING AND SUPPORT INCLUDING:

- Emotional well-being
- Check tolerability of medication
- Monitor glycemic status
- Biofeedback including SMBG, weight, step count, HbA_{1c}, blood pressure, lipids

REVIEW AND AGREE ON MANAGEMENT PLAN

- Review management plan
- Mutual agreement on changes
- Ensure agreed modification of therapy is implemented in a timely fashion to avoid clinical inertia
- Decision cycle undertaken regularly (at least once/twice a year)

ASCVD = Atherosclerotic Cardiovascular Disease
CKD = Chronic Kidney Disease
HF = Heart Failure
DSMES = Diabetes Self-Management Education and Support
SMBG = Self-Monitored Blood Glucose



Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

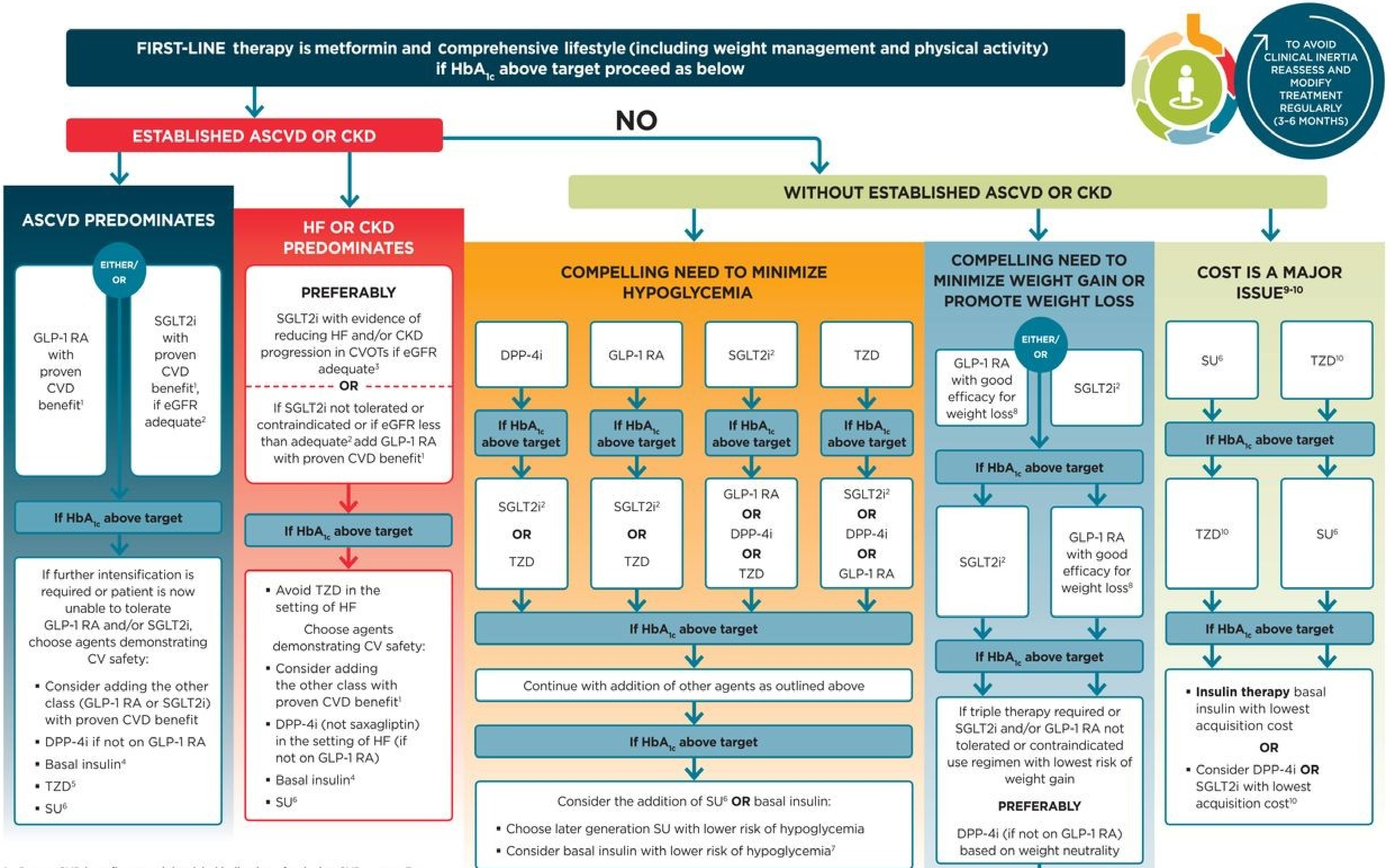
If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin§	or GLP-1-RA	or Insulin§	or GLP-1-RA
or Insulin§	or Insulin§		or Insulin§		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)



FIRST-LINE therapy is metformin and comprehensive lifestyle (including weight management and physical activity) if HbA_{1c} above target proceed as below

TO AVOID CLINICAL INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3-6 MONTHS)

ESTABLISHED ASCVD OR CKD

NO

ASCVD PREDOMINATES

EITHER/OR

- GLP-1 RA with proven CVD benefit[1]
- SGLT2i with proven CVD benefit[1], if eGFR adequate[2]

If HbA_{1c} above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:

- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin[4]
- TZD[5]
- SU[6]

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate[3]

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate[2] add GLP-1 RA with proven CVD benefit[1]

If HbA_{1c} above target

- Avoid TZD in the setting of HF

Choose agents demonstrating CV safety:

- Consider adding the other class with proven CVD benefit[1]
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin[4]
- SU[6]

WITHOUT ESTABLISHED ASCVD OR CKD

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i	GLP-1 RA	SGLT2i[2]	TZD
If HbA_{1c} above target	**If HbA_{1c} above target**	**If HbA_{1c} above target**	**If HbA_{1c} above target**
SGLT2i[2] **OR** TZD	SGLT2i[2] **OR** TZD	GLP-1 RA **OR** DPP-4i **OR** TZD	SGLT2i[2] **OR** DPP-4i **OR** GLP-1 RA

If HbA_{1c} above target

Continue with addition of other agents as outlined above

If HbA_{1c} above target

Consider the addition of SU[6] **OR** basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[7]

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/OR

- GLP-1 RA with good efficacy for weight loss[8]
- SGLT2i[2]

If HbA_{1c} above target

- SGLT2i[2]
- GLP-1 RA with good efficacy for weight loss[8]

If HbA_{1c} above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

- SU[6]
- TZD[5]
- Basal insulin

COST IS A MAJOR ISSUE[9-10]

SU[6]	TZD[10]
If HbA_{1c} above target	
TZD[10]	SU[6]
If HbA_{1c} above target	

- **Insulin therapy** basal insulin with lowest acquisition cost

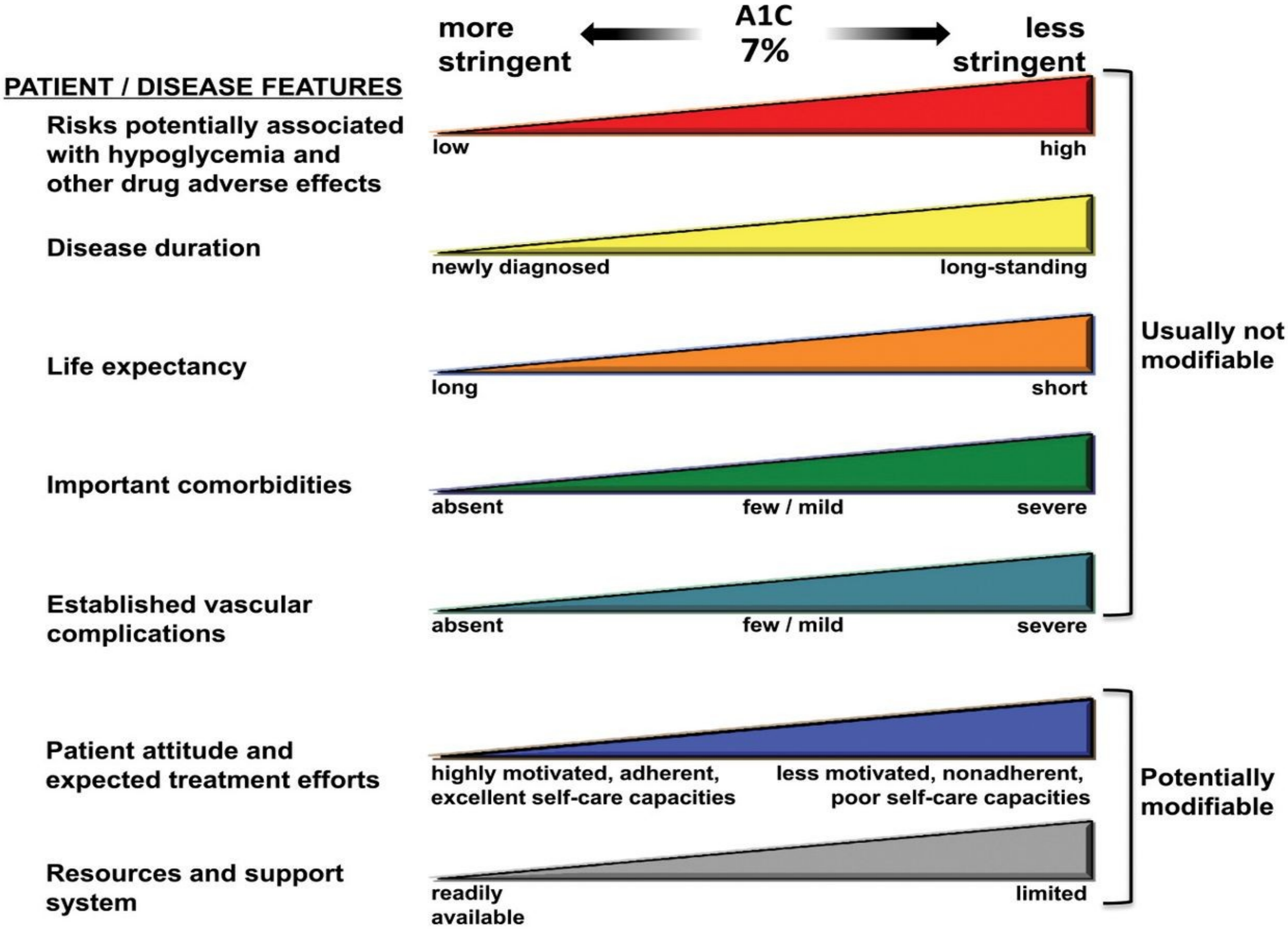
OR

- Consider DPP-4i **OR** SGLT2i with lowest acquisition cost[10]

---

1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Approach to the management of hyperglycemia



more stringent ← A1C 7% → less stringent

PATIENT / DISEASE FEATURES

	more stringent		less stringent
Risks potentially associated with hypoglycemia and other drug adverse effects	low		high
Disease duration	newly diagnosed		long-standing
Life expectancy	long		short
Important comorbidities	absent	few / mild	severe
Established vascular complications	absent	few / mild	severe
Patient attitude and expected treatment efforts	highly motivated, adherent, excellent self-care capacities		less motivated, nonadherent, poor self-care capacities
Resources and support system	readily available		limited

Usually not modifiable: Risks potentially associated with hypoglycemia and other drug adverse effects; Disease duration; Life expectancy; Important comorbidities; Established vascular complications

Potentially modifiable: Patient attitude and expected treatment efforts; Resources and support system

Glycemic recommendations for non-pregnant adults with diabetes

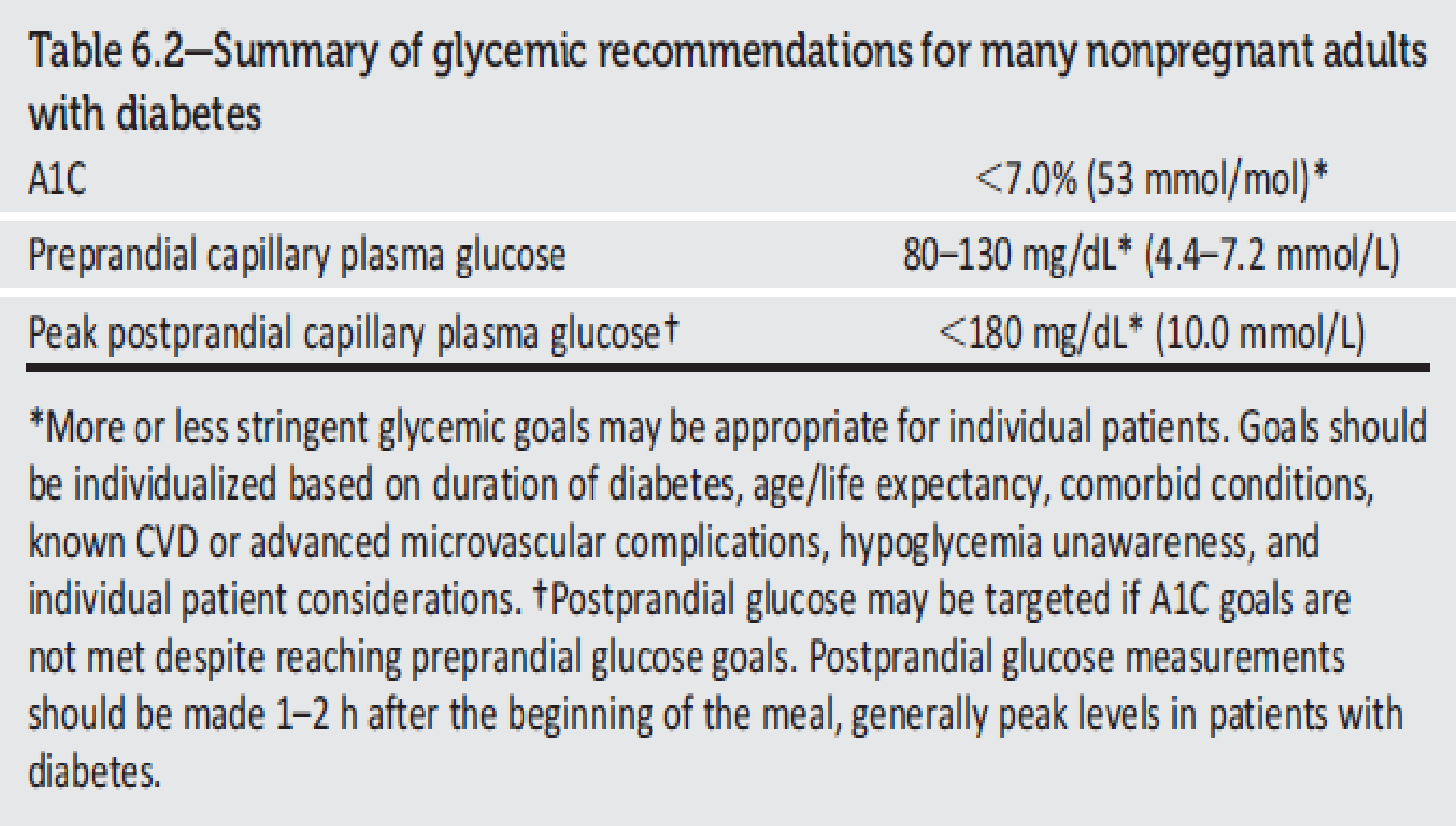


Table 6.2—Summary of glycemic recommendations for many nonpregnant adults with diabetes

A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

*More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations. †Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

Patient with Establish DM

In patients with known diabetes, inquire about:

- **Duration:** Chronic complications of DM are related duration.
- **Care** the patient is currently receiving for the disease.
- **Type** of DM: T1DM or T2DM? Consider other types such as Gestational diabetes and LADA.
- **Age** of onset
- **Manner** of diagnosis - Routine Tests or Symptomatic, if symptomatic explore presenting symptoms

Patient with Establish DM

A focused diabetes history should also include:

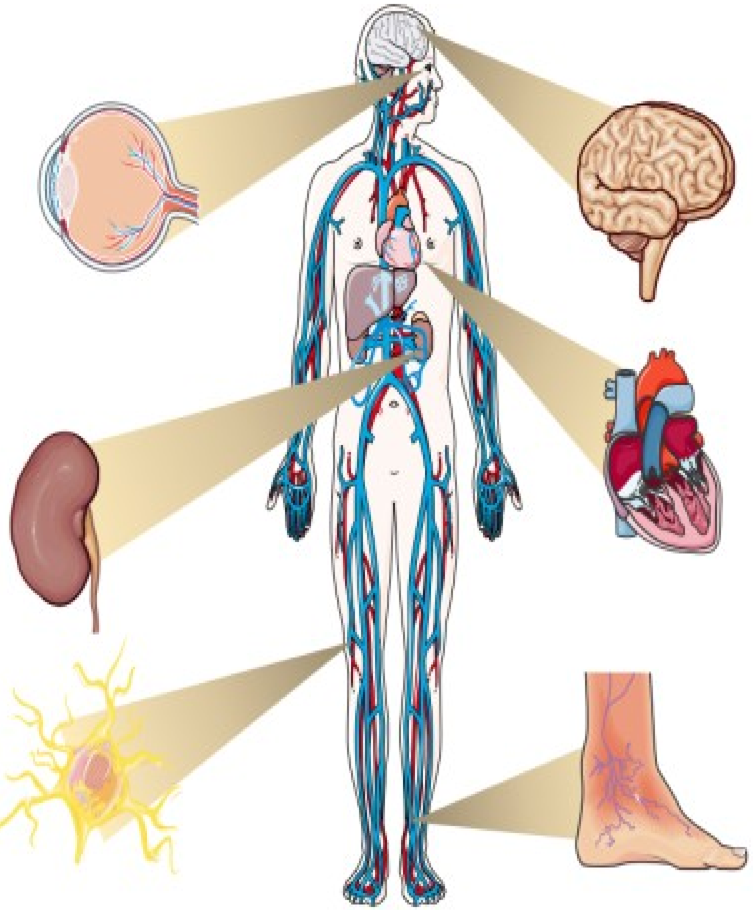
Glucose Control

Frequency of monitoring

Values - Usually pre & 2hrs PP

Poor Control → Complications

Major Complications of Diabetes



Microvascular

Eye

High blood glucose and high blood pressure can damage eye blood vessels, causing retinopathy, cataracts and glaucoma

Kidney

High blood pressure damages small blood vessels and excess blood glucose overworks the kidneys, resulting in nephropathy.

Neuropathy

Hyperglycemia damages nerves in the peripheral nervous system. This may result in pain and/or numbness. Feet wounds may go undetected, get infected and lead to gangrene.

Macrovascular

Brain

Increased risk of stroke and cerebrovascular disease, including transient ischemic attack, cognitive impairment, etc.

Heart

High blood pressure and insulin resistance increase risk of coronary heart disease

Extremities

Peripheral vascular disease results from narrowing of blood vessels increasing the risk for reduced or lack of blood flow in legs. Feet wounds are likely to heal slowly contributing to gangrene and other complications.

Acute Diabetic Complications

- Hypoglycemia
- DKA
- Hyperosmolar

What is Hypoglycemia?

- Symptoms consistent with hypoglycemia in the presence of low plasma glucose that resolve with normalization of plasma glucose level

Classification of hypoglycemia

Level	Glycemic criteria/description
Level 1	Glucose ˂ 70 mg/dL and glucose ≥ 54 mg/dL
Level 2	Glucose ˂ 54 mg/dL
Level 3	A severe event characterized by altered mental and/or physical status requiring assistance

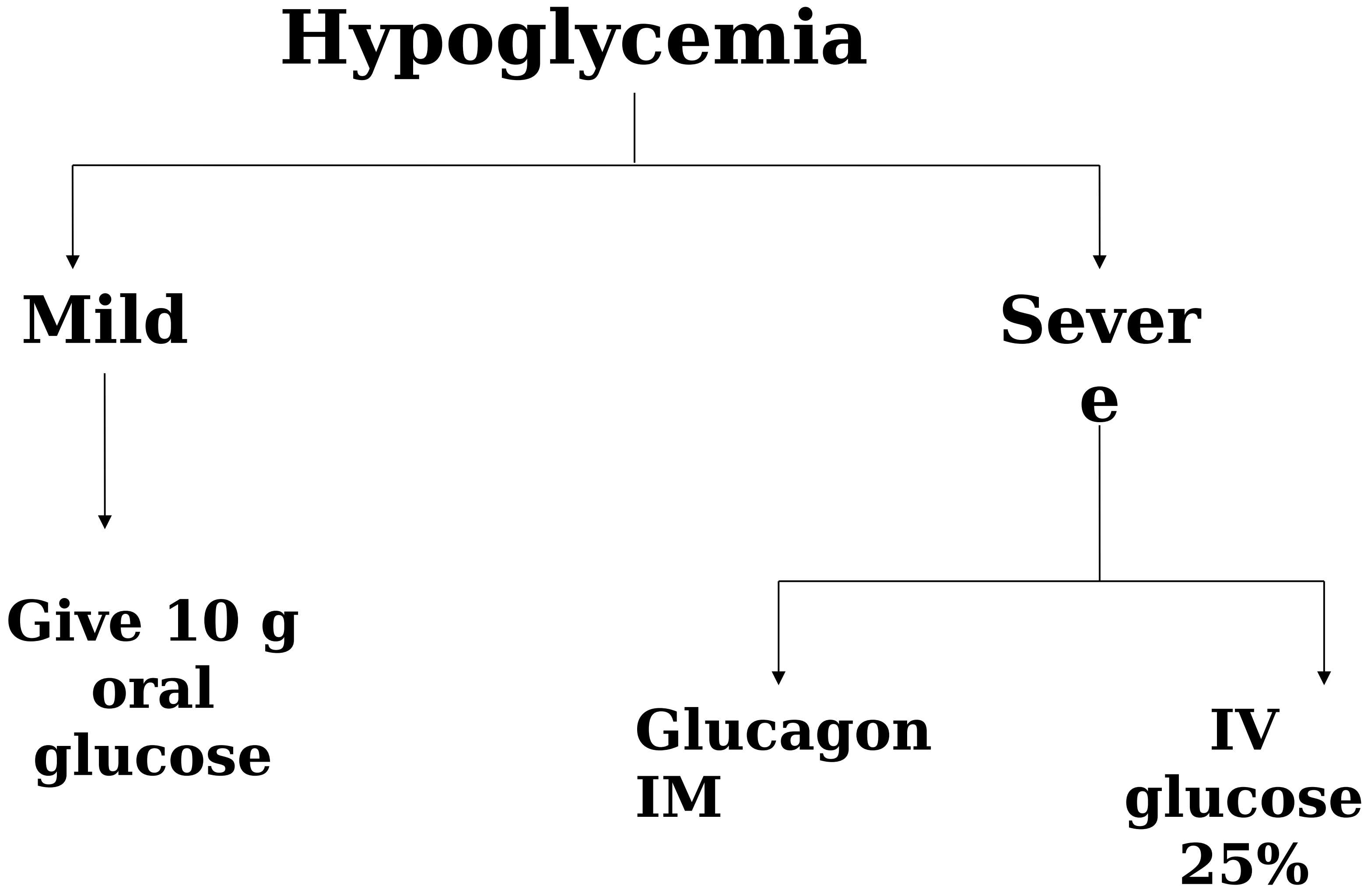
Symptoms according to frequency:

- Sweating.
- Trembling.
- Difficulty in concentration.
- Weakness.
- Visual changes.
- Hunger.
- Palpitation.
- Dizziness.
- Difficulty in speaking.
- Periorbital tingling.
- Headache.

Risk for hypoglycemia on insulin therapy:

- Excessive insulin.
- Wrong type of insulin.
- Missing meal or snacks.
- Excessive exercise.

Therapy



Hypoglycemia

Mild

Give 10 g oral glucose

Severe

Glucagon IM

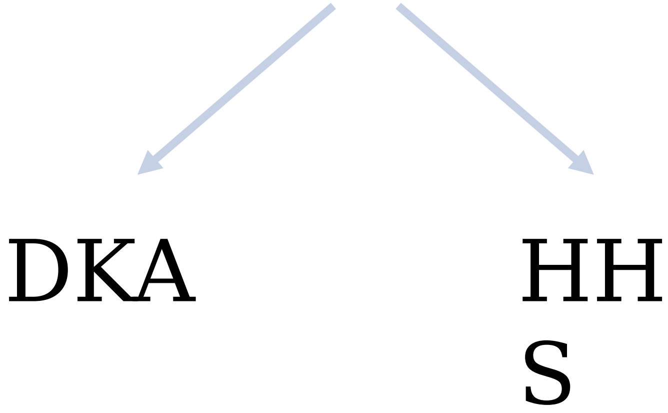
IV glucose 25%

Hypoglycemia

- Glucose (15–20 g) is treatment for the conscious individual with hypoglycemia
- Repeat treatment If SMBG 15 min after shows continued hypoglycemia.
- Once SMBG glucose returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia.

Acute complications

Hyper-glycemia



DKA

HHS

Diabetic ketoacidosis (DKA)

- DKA is caused by severe insulin deficiency & increased counter-regulatory hormones
- Occurs in type 1 >>> type 2
- DKA:
  - Hyperglycaemia,
  - elevated blood levels of ketone bodies (ketosis)
  - acidosis (blood pH becoming acidic)
- Around 25% of cases of DKA are newly diagnosed type 1 diabetes patients

DKA: symptoms and treatment

- The main clinical features of DKA are:
  - dehydration
  - hyperventilation
  - drowsiness
  - vomiting
  - hypothermia
- Initial management:
  - rehydration
  - insulin replacement
  - Correction of electrolytes disturbance and acidosis

Hyperosmolar Hyperglycemic Syndrome (HHS)

- Usually occurs in older people as a result of acute illness or drug therapy
- Hyperglycaemic emergency of type 2 diabetes
- Although insulin levels prevent lipolysis and ketogenesis, hyperglycaemia ensues
- Patients are generally very dehydrated, elderly and frail
- Treatment is mainly rehydration and insulin

Components of the comprehensive diabetes medical evaluation

Medical history

- Age and characteristics of onset of diabetes (e.g., diabetic ketoacidosis, asymptomatic laboratory finding)
- Eating patterns, nutritional status, weight history, sleep behaviors (pattern and duration), and physical activity habits; nutrition education and behavioral support history and needs
- Complementary and alternative medicine use
- Presence of common comorbidities and dental disease
- Screen for depression, anxiety, and disordered eating using validated and appropriate measures
- Screen for diabetes distress using validated and appropriate measures

Components of the comprehensive diabetes medical evaluation

Medical history

- Screen for psychosocial problems and other barriers to diabetes self-management, such as limited financial, logistical, and support resources
- History of tobacco use, alcohol consumption, and substance use
- Diabetes education, self-management, and support history and needs
- Review of previous treatment regimens and response to therapy (A1C records)
- Assess medication-taking behaviors and barriers to medication adherence
- Results of glucose monitoring and patient’s use of data
- Diabetic ketoacidosis frequency, severity, and cause

Components of the comprehensive diabetes medical evaluation

Medical history

- Hypoglycemia episodes, awareness, and frequency and causes
- History of increased blood pressure, abnormal lipids
- Microvascular complications: retinopathy, nephropathy, and neuropathy (sensory, including history of foot lesions; autonomic, including sexual dysfunction and gastroparesis)
- Macrovascular complications: coronary heart disease, cerebrovascular disease, and peripheral arterial disease
- For women with childbearing capacity, review contraception and preconception planning

Components of the comprehensive diabetes medical evaluation

Physical examination

- Height, weight, and BMI; growth and pubertal development in children and adolescents
- Blood pressure determination, including orthostatic measurements when indicated
- Fundoscopic examination
- Thyroid palpation
- Skin examination (e.g., for acanthosis nigricans, insulin injection or infusion set insertion sites)
- Comprehensive foot examination
  - Inspection
  - Palpation of dorsalis pedis and posterior tibial pulses
  - Presence/absence of patellar and Achilles reflexes
  - Determination of proprioception, vibration, and monofilament sensation

Components of the comprehensive diabetes medical evaluation

Laboratory evaluation

- A1C, if the results are not available within the past 3 months
- If not performed/available within the past year
  - Fasting lipid profile, including total, LDL, and HDL cholesterol and triglycerides, as needed
  - Liver function tests
  - Spot urinary albumin–to–creatinine ratio
  - Serum creatinine and estimated glomerular filtration rate
  - Thyroid-stimulating hormone in patients with type 1 diabetes

Thank You